REMARKS

A. Status of the Claims

Claims 3 and 4 were pending at the issuance of the instant Office Action mailed on March 27, 2008. Claims 3 and 4 are rejected in the instant Office Action. No claims are amended, added, or canceled herein. The rejections of the Office Action are traversed for the reasons set forth below.

B. Rejections under 35 USC §103

Claims 3 and 4 are rejected under 35 USC §103 as being unpatentable over Bressi *et al.* In particular, the Action asserts that one of skill in the art would have been motivated to use the compound of the instant claims to treat macular degeneration and diabetic retinopathy based on the teachings in Bressi *et al.* Applicants respectfully traverse.

The Action alleges that Bressi *et al.* teach the use of HDAC inhibitors for the treatment of abnormal angiogenic conditions, including macular degeneration and diabetic retinopathy. The Action further alleges that one of skill in the art would have found "the substitution of one HDAC inhibitor for another" to be obvious absent evidence to contrary.

As stated in MPEP 2143(B), "the rationale to support a conclusion that the claim would have been obvious is that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." As stated in MPEP 2143.02(II), "obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness" (citing *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)).

Applicants respectfully submit, based on the following discussion, that one of skill in the art would not have considered substitution of any of the Bressi compounds with one of the compounds of the instant claims to yield predictable results or to have a reasonable expectation of success.

Bressi *et al.* teach a multitude of HDAC inhibitors, all of which are related by the general formula shown in the Abstract of US Patent No. 7,154,002 ("the '002 patent"). As discussed in Col. 53, Example 3, of the '002 patent, Bressi *et al.* demonstrated that the compounds had varying activities against the HDAC8 isoform, where only some had better than 5 μM activity (see Figures 5A and 5B). The Bressi compounds were not tested for activity against other HDACs. Even though Bressi *et al.* mention that the compounds may be used as inhibitors of Class I HDACs (Col. 11, lines 52-54), there is absolutely no evidence that such compounds can inhibit any of the isoforms in Class I other than HDAC8 (*i.e.* HDAC1, 2, 3, or 11). Further, Bressi *et al.* mention (but do not claim) several examples of HDAC inhibitors, such as SAHA; however, only the claimed compounds are taught to be useful for treating the various diseases listed in the Bressi patent. Thus, Bressi *et al.* teach that a *specific* genus of HDAC inhibitors active against HDAC8 are useful for treating macular degeneration and diabetic retinopathy, but do not teach that *all* HDAC inhibitors are useful for such a purpose. Therefore, one of skill in the art could not have known whether it was activity against HDAC8 specifically or against any HDAC isoform (or any combination of HDAC isoforms) that would be useful for treating the many diseases listed in the Bressi patent. Consequently, based on the teaching by Bressi *et al.*, use of inhibitors against an HDAC isoform(s) other than HDAC8 would not have been predictable.

As pointed out by Bressi *et al.*, numerous human HDACs were known at the time the Bressi application was filed, and were categorized into three distinct classes (see col. 11, lines 55-67). As discussed in the Response to the Office Action mailed October 15, 2007, HDAC inhibitors do not simply inhibit HDACs, but can also inhibit enzymes that catalyze the acetylation of non-histone proteins, including transcription factors, cytoskeletal proteins, and chaperones (see for example Di Gennaro *et al.*, *Amino Acids* **2004**, *26*(4), 435-441; and Konstantinopoulos *et al.*, *Expert Opinion Investigational Drugs* **2007**, *16*(5), 569-571, abstracts submitted previously). It is well established that not all of the HDAC inhibitors share exactly the same activity (*e.g.* some are selective for particular HDAC isoforms, while others non-selectively act on multiple isoforms), and that different HDAC isoforms can regulate different sets of genes. Consequently, the universe of HDAC inhibitors is diverse and very large, and substitution of one HDAC inhibitor for another would not necessarily lead to a predictable result, unless the two inhibitors were already known to have the exact

same activity profile (*e.g.* acts on the exact same isoform or combination of isoforms and/or regulates the same genes).

The instant claims are directed toward a small subset of that very large universe. The Federal Circuit in *Eisai Co. v. Dr. Reddy's Labs* has indicated that

> the Supreme Court's analysis in *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a 'finite number of identified, predictable solutions." (*Eisai Co. v. Dr. Reddy's Labs, Ltd.*, 487 USPQ2d 1452 (Fed. Cir. 2008) citing *KSR Int'l Co. v. Teleflex*, 127 S. Ct. at 1742.

Bressi *et al.* certainly did not provide such reasons for narrowing the HDAC inhibitor universe to the compounds of the instant claims. Applicants submit that there is no teaching or suggestion in the '002 patent, or in the art at the time the instant application was filed, that would have motivated one of skill in the art to select the particular compounds of the instant claims to treat an ocular neovascular or edematous disease, particularly since (1) the compounds of the instant claims are not structurally related to the Bressi compounds, and (2) Bressi *et al.* did not teach or suggest that the compounds of the instant claims had the same activity as the Bressi compounds. The Action does not set forth any specific evidence or reasoning that would demonstrate otherwise.

Since Bressi *et al.* disclosed many examples of HDAC inhibitors, but only indicated that the specifically claimed compounds were useful for treating diseases listed in the Bressi patent, Applicants respectfully submit that the Action should provide more than the conclusory statement relating to substitution of one HDAC inhibitor for another to establish a prima facie case of obviousness[1].

In conclusion, Applicants submit that it would not have been obvious to simply substitute one of the claimed compounds for one of the Bressi compounds, because Bressi *et al.* teach a very specific family of HDAC inhibitors that are structurally unrelated to the

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[1] The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 550 U.S. at ___ , 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval). MPEP 2142

compounds of the instant invention, and which were not shown to have the same activity profile as the instantly claimed compounds. Further, there is no teaching or suggestion in Bressi *et al.* that *any* HDAC inhibitor would be useful for treating the various diseases taught in the '002 patent. Rather, Bressi *et al.* emphasize that the particular compounds of the '002 patent claims (which specifically act on HDAC8) are useful for such treatments, not the other HDAC inhibitors that are disclosed but not claimed in the Bressi *et al.* patent. Thus, there is no reasonable expectation of success for substituting one HDAC inhibitor for another, absent specific evidence to the contrary.

Therefore, Applicants submit that the claims are not obvious over Bressi *et al.*, and respectfully request that this ground of rejection be withdrawn.

D. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (817) 615-5330 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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